

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

|  |  |
|--|--|
| <b>Date of mailing (day/month/year)</b><br>18 August 2000 (18.08.00)             |  |
| <b>International application No.</b><br>PCT/JP99/07161                           | <b>Applicant's or agent's file reference</b><br>09333                |
| <b>International filing date (day/month/year)</b><br>20 December 1999 (20.12.99) | <b>Priority date (day/month/year)</b><br>24 December 1998 (24.12.98) |
| <b>Applicant</b><br>UENO, Ryuji  |  |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

09 June 2000 (09.06.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

|  |   |
|--|---|
| <b>The International Bureau of WIPO</b><br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | <b>Authorized officer</b><br><br>Antonia Muller |
| Facsimile No.: (41-22) 740.14.35   | Telephone No.: (41-22) 338.83.38                |

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|   |           |   |
|---|-----------|---|
| <b>(51) International Patent Classification <sup>7</sup> :</b><br><b>A61K 38/13, 31/436, A61P 27/02</b>   | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 00/38703</b><br><b>(43) International Publication Date:</b> 6 July 2000 (06.07.00)  |
| <b>(21) International Application Number:</b> PCT/JP99/07161<br><b>(22) International Filing Date:</b> 20 December 1999 (20.12.99)<br><br><b>(30) Priority Data:</b><br>60/113,939 24 December 1998 (24.12.98) US<br><br><b>(71) Applicants (for all designated States except US):</b> R-TECH UENO, LTD. [JP/JP]; 2-4-8, Koraihashi, Chuo-ku, Osaka-shi, Osaka 541-8543 (JP). FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).<br><br><b>(72) Inventor; and</b><br><b>(75) Inventor/Applicant (for US only):</b> UENO, Ryuji [JP/US]; 9476 Turnberry Drive, Potomac, Montgomery, MD 20854 (US).<br><br><b>(74) Agent:</b> TAKASHIMA, Hajime; Yuki Bldg., 3-9, Hiranomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-0046 (JP). |           | <b>(81) Designated States:</b> AL, AU, BR, CA, CN, CZ, HU, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, RO, RU, SI, TR, US, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).<br><br><b>Published</b><br><i>With international search report.<br/>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| <b>(54) Title:</b> AGENT FOR TREATING VISUAL CELL FUNCTION DISORDER   |           |   |
| <b>(57) Abstract</b><br><br>The present invention provides an agent for treating visual cell function disorder containing an interleukin inhibitor such as macrolide compound, particularly FK506.  |           |   |

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

|    |                          |    |                                       |    |   |    |                          |
|----|--------------------------|----|---------------------------------------|----|---|----|--------------------------|
| AL | Albania                  | ES | Spain                                 | LS | Lesotho                                   | SI | Slovenia                 |
| AM | Armenia                  | FI | Finland                               | LT | Lithuania                                 | SK | Slovakia                 |
| AT | Austria                  | FR | France                                | LU | Luxembourg                                | SN | Senegal                  |
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| AZ | Azerbaijan               | GB | United Kingdom                        | MC | Monaco                                    | TD | Chad                     |
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| BB | Barbados                 | GH | Ghana                                 | MG | Madagascar                                | TJ | Tajikistan               |
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| BG | Bulgaria                 | HU | Hungary                               | ML | Mali                                      | TT | Trinidad and Tobago      |
| BJ | Benin                    | IE | Ireland                               | MN | Mongolia                                  | UA | Ukraine                  |
| BR | Brazil                   | IL | Israel                                | MR | Mauritania                                | UG | Uganda                   |
| BY | Belarus                  | IS | Iceland                               | MW | Malawi                                    | US | United States of America |
| CA | Canada                   | IT | Italy                                 | MX | Mexico                                    | UZ | Uzbekistan               |
| CF | Central African Republic | JP | Japan                                 | NE | Niger                                     | VN | Viet Nam                 |
| CG | Congo                    | KE | Kenya                                 | NL | Netherlands                               | YU | Yugoslavia               |
| CH | Switzerland              | KG | Kyrgyzstan                            | NO | Norway                                    | ZW | Zimbabwe                 |
| CI | Côte d'Ivoire            | KP | Democratic People's Republic of Korea | NZ | New Zealand                               |    |                          |
| CM | Cameroon                 |    |                                       | PL | Poland                                    |    |                          |
| CN | China                    | KR | Republic of Korea                     | PT | Portugal                                  |    |                          |
| CU | Cuba                     | KZ | Kazakstan                             | RO | Romania                                   |    |                          |
| CZ | Czech Republic           | LC | Saint Lucia                           | RU | Russian Federation                        |    |                          |
| DE | Germany                  | LI | Liechtenstein                         | SD | Sudan                                     |    |                          |
| DK | Denmark                  | LK | Sri Lanka                             | SE | Sweden                                    |    |                          |
| EE | Estonia                  | LR | Liberia                               | SG | Singapore                                 |    |                          |

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|   |   |  |
|---|---|--|
| Applicant's or agent's file reference<br><b>09333</b>   | <b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |  |
| International application No.<br><b>PCT/JP 99/07161</b> | International filing date (day/month/year)<br><b>20/12/1999</b>   | (Earliest) Priority Date (day/month/year)<br><b>24/12/1998</b> |
| Applicant<br><br><b>R-TECH UENO, LTD. et al.</b>        |   |  |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

## 4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

## 5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

## 6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 99/07161

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP 99/07161

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## TENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING  
SUBMISSION OR TRANSMITTAL  
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

TAKASHIMA, Hajime  
Yuki Bldg.  
3-9, Hiranomachi 3-chome  
Chuo-ku  
Osaka-shi, Osaka 541-0046  
JAPON

|  |   |
|--|---|
| Date of mailing (day/month/year)<br>20 March 2000 (20.03.00)         |   |
| Applicant's or agent's file reference<br>09333                       | IMPORTANT NOTIFICATION  |
| International application No.<br>PCT/JP99/07161                      | International filing date (day/month/year)<br>20 December 1999 (20.12.99) |
| International publication date (day/month/year)<br>Not yet published | Priority date (day/month/year)<br>24 December 1998 (24.12.98)             |
| Applicant<br>R-TECH UENO, LTD. et al                                 |   |

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

| <u>Priority date</u>    | <u>Priority application No.</u> | <u>Country or regional Office<br/>or PCT receiving Office</u> | <u>Date of receipt<br/>of priority document</u> |
|-------------------------|---------------------------------|---|---|
| 24 Dece 1998 (24.12.98) | 60/113,939                      | US  | 17 Marc 2000 (17.03.00)                         |

|  |                                    |
|--|------------------------------------|
| The International Bureau of WIPO<br>34, chemin des C. lombettes<br>1211 Geneva 20, Switz rland | Authorized officer<br>Taïeb Akremi |
| Facsimile No. (41-22) 740.14.35  | Telephone No. (41-22) 338.83.38    |

# TENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

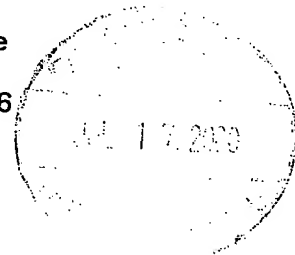
**PCT**

## NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

TAKASHIMA, Hajime  
Yuki Bldg.  
3-9, Hiranomachi 3-chome  
Chuo-ku  
Osaka-shi, Osaka 541-0046  
JAPON



|   |   |   |  |
|---|---|---|--|
| Date of mailing (day/month/year)<br>06 July 2000 (06.07.00) |   | <b>IMPORTANT NOTICE</b>                                       |  |
| Applicant's or agent's file reference<br>09333              |   |   |  |
| International application No.<br>PCT/JP99/07161             | International filing date (day/month/year)<br>20 December 1999 (20.12.99) | Priority date (day/month/year)<br>24 December 1998 (24.12.98) |  |
| Applicant<br>R-TECH UENO, LTD. et al                        |   |   |  |

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:  
**AU,CN,JP,KR,US**

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:  
**AL,BR,CA,CZ,EP,HU,IL,IN,LT,LV,MK,MX,NO,NZ,RO,RU,SI,TR,ZA**

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 06 July 2000 (06.07.00) under No. WO 00/38703

### REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

### REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

|  |   |
|--|---|
| The International Bureau of WIPO<br>34, chemin des Cornettes<br>1211 Geneva 20, Switzerland<br><br>Facsimile No. (41-22) 740.14.35 | Authorized officer<br><br>J. Zahra<br><br>Telephone No. (41-22) 338.83.38 |
|--|---|



Continuation of Form PCT/IB/308

**NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF  
THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES**

|   |  |
|---|--|
| <b>Date of mailing (day/month/year)</b><br>06 July 2000 (06.07.00)  | <b>IMPORTANT NOTICE</b>                                |
| <b>Applicant's or agent's file reference</b><br>09333   | <b>International application No.</b><br>PCT/JP99/07161 |
| <p>The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.</p> |  |

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 11 APR 2001



|   |   |  |
|---|---|--|
| Applicant's or agent's file reference<br>09333  | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |  |
| International application No.<br>PCT/JP99/07161   | International filing date (day/month/year)<br>20/12/1999  | Priority date (day/month/year)<br>24/12/1998 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K38/13 |   |  |
| Applicant<br>R-TECH UENO, LTD. et al.   |   |  |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
  - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

|   |   |
|---|---|
| Date of submission of the demand<br><br>09/06/2000  | Date of completion of this report<br><br>09.04.2001   |
| Name and mailing address of the international preliminary examining authority:<br><br> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br><br>Blott, C<br><br>Telephone No. +49 89 2399 7538<br><br> |

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

The wording "an agent for treating visual cell function disorder comprising an interleukin 2 inhibitor" and the generic term "macrolide compound" relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Moreover, present claim 1 relates to compounds defined by reference to a pharmacological mechanism of action "compound which inhibits interleukin 2". The definition of compounds by reference to a pharmacological mechanism in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to fully compare the parameters the applicant has chosen to employ with what is set out in the prior art.

Also the definition "visual cell function disorder" is considered obscure, not defining a specific disease recognized in the art to which the invention belongs.

Therefore, present claim 1 and 2 and the corresponding dependent claims, relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, concise, supported and disclosed, namely for the compounds defined by Markush formula (I) in claim 3 and the compounds explicitly mentioned in the description at pages 8-11 and in claim 4, in respect to the diseases explicitly mentioned in claims 5-7 and in the description at pages 11, with due regard to the general idea underlying the application.

All claims 1 to 10 have been searched incompletely.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP99/07161

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-15 as originally filed

**Claims, No.:**

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP99/07161

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-10 (all in parts).

because:

- ☒ the said international application, or the said claims Nos. 9 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
  - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
  - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
  - ☒ no international search report has been established for the said claims Nos. 1-10 (all in parts).
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
  - ☐ the computer readable form has not been furnished or does not comply with the standard.

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

|                               |                                |
|-------------------------------|--------------------------------|
| Novelty (N)                   | Yes: Claims                    |
|                               | No: Claims 1-10                |
| Inventive step (IS)           | Yes: Claims                    |
|                               | No: Claims 1-10                |
| Industrial applicability (IA) | Yes: Claims see separate sheet |

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/JP99/07161

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No:      Claims

2. Citations and explanations  
**see separate sheet**

**VI.      Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**SECTION III**

1. Claims 1-10 relate to an extremely large number of possible compounds and do consequently not meet the requirements of Art. 6 PCT (cf. form PCT/ISA/210, box I.1.). The IPEA will only formulate an assessment of novelty, inventive step and industrial applicability for the part of claims 1-10 for which an International Search Report has been drawn up.
2. Claim 9 relates to a subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Art. 34(4)(a)(i) PCT).

**SECTION V**

3. a) The following documents, which were cited in the International Search Report, are referred to in this report; the numbering will be adhered to in the rest of the procedure:
  - D1: WO 99 00129
  - D2: WO 94 13275
  - D3: WO 96 00073
  - D4: WO 92 03049
  - D5: WO 00 09109
  - D6: EP 0 532 862
  - D7: WO 99 34830
  - D8: IOVS, (MARCH 15, 1998) VOL. 39, NO. 4, PP. S273.
  - D9: INVESTIGATIVE OPHTHALMOLOGY AND VISUAL SCIENCE, (1998 JUN) 39 (7) 1227-32.
  - D10: STROKE (1998), 29(7), 1431-1438
  - D11: J. IMMUNOL. (1995), 154(2), 922-7
  - D12: INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, (1994) VOL. 35, NO. 4, PP. 1923. MEETING INFO.: ANNUAL MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY SARASOTA, FLORIDA, USA MAY 1-6, 1994
  - D13: ARCH. OPHTHALMOL. (CHICAGO) (1986), 104(1), 114-17
- b) D1: see section VI.

c) D2 refers to a method of protecting retinal ganglion cells against glaucoma associated damage by topical administration of an antagonist of glutamate induced excitotoxicity, such as FK-506 (cf. claims 2, 10 and page 13, table 2 page 2).

d) D3 refers to methods of treating optic neuritis and visual impairment by administering a protective agent, which inhibits glutamate-mediated retinal cell damage, such as FK-506 (cf. page 2, lines 6-12 and page 4, lines 24-25). Agents that cannot cross the blood/brain barrier may be administered topically (cf. page 19, lines 28-31).

e) D4 refers to the treatment of T-cell mediated diseases, such as auto-immune uveoretinitis, by administration of a polycyclic aromatic compound, alone or in combination with an immunosuppressive agent, such as cyclosporin A or FK- 506 (cf. claims 1, 4, 11, 12). The compositions may be applied topically (cf. page 11, lines 9-13). Comparative tests were carried out with cyclosporin A as monotherapy (cf. example 3, fig. 4A/B and 5A/B).

f) D5: see section VI.

g) D6 refers to the treatment of ocular inflammation, such as uveitis, e.g. retinitis, by administration of rapamycin (cf. column 1, lines 3-6 and lines 35- 44). Administration may be topical (cf. claim 4). Cyclosporin A is known to be effective in chronic idiopathic uveitis and was used in the comparative tests (cf. column 2, lines 37-41 and example 1).

h) D7: see section VI.

i) D8 refers to the same test as D10 (cf. item k)).

j) D9 refers to an in-vitro test wherein FK-506 and cyclosporin A displayed protective effects against glutamate neurotoxicity in cultured retinal neurons (cf. abstract).

k) D10 refers to an in-vivo test wherein tacrolimus (=FK506) displayed protective effects on ischemia-induced retinal damage (cf. abstract). FK-506 was injected intramuscularly to rats after induction of ischemia (cf. page 1432 Animal model).



l) D11 discloses synergistic effects of rapamycin and cyclosporin A in the treatment of experimental autoimmune uveoretinitis (EAU) (cf. abstract). The drugs are administered parenterally (cf. page 923, last paragraph). FK-506 is already known to be effective for treating uveitis and rapamycin for treating EAU (cf. page 922).

m) D12 refers to an in-vivo test wherein a sustained release device containing dexamethasone (DEX) and cyclosporine (CsA) lessened the severity of experimental proliferative vitreoretinopathy.

n) D13 refers to an in-vivo test, wherein cyclosporine reduced intraocular inflammation in EAU. Cyclosporine was administered by i.m. injection (page 114, abstract).

4. Novelty

**The following assessment of novelty only applies for the parts of the present claims for which an International Search Report has been drawn up (cf. section III 1.)**

a) Rapamycin, FK-506 and cyclosporines are already well known therapeutical agents to the man skilled in the art (cf. item 3.c-e),g,i-n)). Furthermore, their use in the treatment of visual cell function disorders, such as e.g. for reduction of retinal ganglion cell damage, is already known from the prior art (cf. item 3.d)). Anyhow, even if the therapeutical use was new, it would not render said agents new. Moreover, topical administration to the eye of said compounds is also known from the prior art (cf. item 3.c-e),g)).

It is pointed out that the term "retinopathy" in claims 5-7 has not been defined in the present application. It is assumed that retinopathy is any non-inflammatory disease of the retina (cf. Dorland's illustrated Medical Dictionary, 26th edition, page 1148) and it has been supposed that e.g. the retinal ganglion cells damage described in D3 falls within the definition of retinopathies.

Hence, the subject-matter of claims 1-8 is not new over the prior art (Art. 33(2) PCT).

b) None of the above-mentioned documents discloses nor anticipates the use of an

agent according to claims 1-4 for the treatment of ischemic retinopathy, respectively diabetic retinopathy.

c) As already mentioned under item a), the agents of claims 1-8 and their use for the treatment of visual cell function disorders is already known from the prior art. The subject-matter of claim 9, i.e. a method of treating visual cell function disorder, and the subject-matter of claim 10, i.e. the use of an interleukin 2 inhibitor for treating visual cell function disorder, is therefore not new over the prior art (Art. 33(2) PCT).

5. Inventive step

**The following assessment of inventive step only applies for the parts of the present claims for which an International Search Report has been drawn up (cf. section III 1.)**

D10, which is considered to represent the most relevant state of the art, refers, as already mentioned under item V 3.k), to an in-vivo test wherein FK-506 displayed protective effects on ischemia-induced retinal damage (cf. abstract).

The man skilled in the art would derive from D10 that FK-506 may be useful in the treatment of ischemia-induced retinal damage, including any type of ischemic retinopathies such as e.g. diabetic retinopathy.

Thus, the subsequent therapeutic application of an agent according to claims 1-4 for the treatment of ischemic retinopathy, respectively diabetic retinopathy is already suggested by D10.

6. Industrial applicability

For the assessment of the present claim 9 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**SECTION VI**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/JP99/07161

7. Certain published documents (Rule 70.10)

| Application No<br>Patent No | Publication date<br>(day/month/year) | Filing date<br>(day/month/year) | Priority date (valid claim)<br>(day/month/year) |
|-----------------------------|--------------------------------------|---------------------------------|---|
| WO 99/00129 (D1)            | 07.01.99                             | 15.06.98                        | 30.06.97  |
| WO 00/09109 (D5)            | 24.02.00                             | 12.08.99                        | 14.08.98  |
| WO 99/34830 (D7)            | 15.07.99                             | 17.12.98                        | 30.12.97  |

a) D1 refers to the treatment of proliferative vitreoretinopathy by administration of an antagonist of glutamate induced excitotoxicity, such as FK-506 (cf. page 1, lines 3-5, page 5, lines 25-27 and page 8, table 1, page 2). Administration may be topical (cf. claim 10). D1 may anticipate the subject-matter of claims 1-5 and 8-10.

b) D5 refers to the treatment of vision disorders such as disorders of the retina, e.g. diabetic retinopathy or retinal ischemia-induced eye injury, by administration of a pipecolic acid derivative such as rapamycin (cf. claims 1, 5, 7 and page 19, lines 18-30). The compounds are preferably administered topically to the skin (cf. page 60, lines 13-14). D5 may anticipate the subject-matter of claims 1-10.

c) D7 refers to preparations for topical ophthalmic application of immunosuppressive agents, such as macrolide antibiotics e.g. tacrolimus and cyclosporins (cf. claim 1 and page 41, lines 18-22). The preparations may be used in the treatment of e.g. endogenous uveitis (cf. page 2, line 11). D7 may anticipate the subject-matter of claims 1-4 and 8-10.

**SECTION VII**

8. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2-D4, D6, D9-D11, D13 is not mentioned in the description, nor are these documents identified therein.

## PCT/JP 99/07161

IPC 7 A61K38/13 A61K31/436 A61P27/02

IPC 7 A61K

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## Veronese, A

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 99/07161

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|----------|--|-----------------------|
| X        | WO 92 03049 A (UNIV NEW YORK)<br>5 March 1992 (1992-03-05)<br>claim 4<br>page 8, line 6<br>claims 4,11,12<br>---   | 1-5,8-10              |
| E        | WO 00 09109 A (GUILFORD PHARM INC)<br>24 February 2000 (2000-02-24)<br>claims 1,4,5,7,17<br>---  | 1,2,5-10              |
| X        | EP 0 532 862 A (UNIV LOUISVILLE RES FOUND)<br>24 March 1993 (1993-03-24)<br>column 1, line 32-44; claims 1-10;<br>examples<br>---  | 1,2,5-10              |
| Y        |  | 6-8                   |
| P,X      | WO 99 34830 A (MA & TCARON ;GALENA A S<br>(CZ); STUCHLIK JOSEF (CZ); STUCHLIK MILAN)<br>15 July 1999 (1999-07-15)<br>page 2, paragraphs 1-4; claims<br>page 1, paragraphs 2,3<br>---   | 1-4,8-10              |
| X        | KIRYU, J. (1) ET AL: "In vivo evaluation<br>of the inhibitory effects of tacrolimus<br>(FK506) on leukocyte accumulation during<br>retinal ischemia reperfusion injury."<br>IOVS, (MARCH 15, 1998) VOL. 39, NO. 4, PP.<br>S273. MEETING INFO.: ANNUAL MEETING OF THE<br>ASSOCIATION FOR RESEARCH IN VISION AND<br>OPHTHALMOLOGY FORT LAUDERDALE, FLORIDA,<br>USA MAY 10-15, 1998 ASSOCIATION FOR<br>RESEARCH IN VISION AND OPHTHALMOLOGY.,<br>XP000913707<br>--- | 1-5,9,10              |
| Y        | abstract   | 6-8                   |
| X        | KIKUCHI M ET AL: "Protective effects of<br>FK506 against glutamate-induced<br>neurotoxicity in retinal cell culture."<br>INVESTIGATIVE OPHTHALMOLOGY AND VISUAL<br>SCIENCE, (1998 JUN) 39 (7) 1227-32. ,<br>XP000913706<br>---   | 1-5,9,10              |
| Y        | the whole document   | 6-8                   |
| X        | TSUJIKAWA, AKITAKA ET AL: "Tacrolimus<br>(FK506) attenuates leukocyte accumulation<br>after transient retinal ischemia"<br>STROKE (1998), 29(7), 1431-1438 ,<br>XP000913599<br>---   | 1-5,9,10              |
| Y        | the whole document   | 6-8                   |
|          | ---  |                       |
|          | -/--   |                       |

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|----------|---|-----------------------|
| X        | MARTIN, DANIEL F. ET AL: "Synergistic effect of rapamycin and cyclosporin A in the treatment of experimental autoimmune uveoretinitis"<br>J. IMMUNOL. (1995), 154(2), 922-7 ,<br>XP000907419<br>the whole document<br>---   | 1,2,5-10              |
| X        | PEARSON, P. A. (1) ET AL: "Sustained delivery of cyclosporine (CsA) and dexamethasone (DEX) in the treatment of experimental proliferative vitreoretinopathy."<br>INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, (1994) VOL. 35, NO. 4, PP. 1923.<br>MEETING INFO.: ANNUAL MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY SARASOTA, FLORIDA, USA MAY 1-6, 1994 , XP000913593<br>abstract<br>--- | 1,2,5-10              |
| Y        | abstract<br>---   | 6-8                   |
| X        | STRIPH, GERALD ET AL: "Retina S antigen-induced uveitis. The efficacy of cyclosporine and corticosteroids in treatment"<br>ARCH. OPHTHALMOL. (CHICAGO) (1986), 104(1), 114-17 , XP000913594<br>the whole document<br>-----  | 1,2,5-10              |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 99/07161

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)   | Publication<br>date  |
|---|---------------------|--|--|
| WO 9900129 A                              | 07-01-1999          | AU 7967298 A<br>EP 0994709 A   | 19-01-1999<br>26-04-2000   |
| WO 9413275 A                              | 23-06-1994          | US 5922773 A<br>AU 683634 B<br>AU 5741494 A<br>CA 2150933 A<br>EP 0671910 A<br>JP 8506807 T  | 13-07-1999<br>20-11-1997<br>04-07-1994<br>23-06-1994<br>20-09-1995<br>23-07-1996   |
| WO 9600073 A                              | 04-01-1996          | US 5597809 A<br>AU 711652 B<br>AU 2819695 A<br>CA 2192209 A<br>EP 0797442 A<br>JP 10502340 T   | 28-01-1997<br>21-10-1999<br>19-01-1996<br>04-01-1996<br>01-10-1997<br>03-03-1998   |
| WO 9203049 A                              | 05-03-1992          | AT 147936 T<br>DE 69124380 D<br>DE 69124380 T<br>EP 0544802 A<br>US 5514714 A  | 15-02-1997<br>06-03-1997<br>14-08-1997<br>09-06-1993<br>07-05-1996   |
| WO 0009109 A                              | 24-02-2000          | NONE   |  |
| EP 0532862 A                              | 24-03-1993          | AT 133336 T<br>AU 653415 B<br>AU 2035092 A<br>CA 2074641 A<br>CZ 285660 B<br>DE 69207847 D<br>DE 69207847 T<br>DK 532862 T<br>ES 2083030 T<br>HK 1005705 A<br>HU 211218 B<br>IL 102414 A<br>JP 2568962 B<br>JP 5194212 A<br>MX 9204381 A<br>NZ 243679 A<br>SK 230792 A<br>RU 2048812 C<br>US 5387589 A<br>ZA 9204953 A | 15-02-1996<br>29-09-1994<br>28-01-1993<br>26-01-1993<br>13-10-1999<br>07-03-1996<br>30-05-1996<br>19-02-1996<br>01-04-1996<br>22-01-1999<br>28-11-1995<br>04-08-1996<br>08-01-1997<br>03-08-1993<br>01-02-1993<br>24-06-1997<br>08-05-1996<br>27-11-1995<br>07-02-1995<br>28-04-1993 |
| WO 9934830 A                              | 15-07-1999          | CZ 9704237 A<br>AU 1481399 A   | 14-07-1999<br>26-07-1999   |